Relations between surgical variables, pulmonary regurgitation, right ventricular function, autonomic heart rate control and QRS-duration in adolescents with repaired Tetralogy of Fallot.

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Abstract and Keywords

Background:

Patients with repaired Tetralogy of Fallot have increased risk of arrhythmias, correlating with prolongation of the QRS complex. The underlying mechanisms are uncertain. We explored the relations between different surgical variables, pulmonary regurgitation, right ventricular function, autonomic heart rate control and QRS-duration in adolescents with repaired Tetralogy of Fallot.

Methods and Results:

17 patients (13-18 years) with repaired Tetralogy of Fallot underwent clinical examination, electrocardiogram, echocardiography, exercise testing, testing of autonomic heart rate control and cardiac magnetic resonance imaging. Details of previous surgical procedures were obtained from patients' records. All variables were subjected to multivariate linear regression analyses.

Patients operated with a transannular patch had larger pulmonary regurgitation fraction ($r=18.82$ (1.18;36.46), $p=0.038$). Pulmonary regurgitation was associated with increased right ventricular end diastolic volume ($r=1.37$ (0.86;1.88), $p<0.000$), which in turn was related to longer QRS-duration ($r=0.40$ (0.11;0.70), $p=0.011$). No other significant interrelations were found.

Conclusion:

The use of a transannular patch was the only surgical variable associated with pulmonary regurgitation in our study, in turn leading to right ventricular dilatation and prolongation of the QRS complex.

Key words: Tetralogy of Fallot, transannular patch, autonomic heart rate control, pulmonary regurgitation, right ventricular dilatation, QRS-duration.

Introduction

Surgical repair of Tetralogy of Fallot (ToF) has low mortality, but survival decreases as these patients go into adulthood (1,2), mainly due to sudden cardiac death thought to be caused by sustained ventricular arrhythmia (3). The underlying mechanisms for the increased risk of arrhythmia are yet to be explained in detail.

Pulmonary regurgitation (PR) is a known complication after repair of ToF, well tolerated initially, but eventually leading to right ventricular (RV) dilatation and dysfunction and impaired clinical status (4,5). RV dilatation, in turn, is associated with QRS prolongation late after repair, and a QRS-duration of >180 ms is a recognized risk factor for arrhythmia (3,6). In addition, altered autonomic heart rate control presents a known risk of ventricular arrhythmia in patients with ischemic heart disease, and has been suggested as one of the mechanisms of arrhythmias in patients operated for ToF (7).

In an attempt to identify risk factors of arrhythmia, we have explored the interrelations between different surgical variables, RV volumes and function, PR, autonomic heart rate control and QRS duration. We hypothesized that surgery involving a transannular patch (TAP) would be related to PR and RV dilatation, further leading to altered autonomic heart rate control and prolongation of the QRS complex.

Methods

Patients

Division of Pediatrics, Rikshospitalet University Hospital, Oslo, Norway, is a national referral centre for congenital heart diseases, serving a population of 4.5 million. Repaired ToF patients were recruited from a locally developed, nation-wide database, by the following criteria: a) Age 12-18 years, b) No known arrhythmia, c) No known neurologic sequela d) No chronic disease apart from their congenital heart defect and e) No residual ventricular septal defect.

Written, informed consent was obtained from all participants and their parents. The study was approved by the Regional committee for ethics in medical research.

Clinical, cardiological and autonomic assessment

Details of timing and type of surgery were obtained from the patient records. Initial palliation, age at primary repair, the use of a transannular patch and/or a ventriculotomy, and pulmonary stenosis prior to repair as well as the replacement of the pulmonary valve was noted. Echocardiographic examinations were performed in all participants by an experienced echocardiographist. A standardized 12-lead electrocardiogram was used to assess QRS-duration. In addition, the patients underwent a 24 hour Holter-monitoring. With the exception of one, all patients underwent exercise tolerance testing with recording of maximum O_2-consumption.

Autonomic heart rate control was assessed from 120 s segments of continuous ECG-recordings obtained during rest. In these time segments, beat-to-beat recordings of the RR-interval were converted to 3 Hz time series and subjected to spectral analyses using an autoregressive algorithm. Spectral components were decomposed, and power densities were computed in the low-frequency (LF) band (0.04-0.15 Hz) and the high-frequency (HF) band (0.15-0.5 Hz). In this article, we only report HF-variability (absolute units), which is considered an index of the vagal (parasympathetic) modulation of heart rate (8,9)

Magnetic resonance imaging

MRI was performed using a 1.5 Tesla Siemens scanner (either Magnetom Vision Plus or Magnetom Sonata (Siemens, Erlangen, Germany) with a phased array body coil. Breath-hold cine images in multiple short axis views covering the entire ventricular complex from base to apex with a slice thickness of 6 mm and an interslice gap of 4 mm were acquired with ECG-triggered segmented gradient echo techniques, FLASH or trueFISP (the last available with Magnetom Sonata only). For each patient end-diastolic and end-systolic frames were identified, and were indexed for body surface area. Right ventricular stroke volume and ejection fraction (EF) and pulmonary regurgitation fraction were calculated.

An experienced radiologist, blinded to all information about the patient apart from the diagnosis assessed wall motion in the RVOT. The findings were divided into two categories: Normal and and akinetic/dyskinetic.

Statistical analysis

Statistical analyses were performed using SPSS software version 14.0. (SPSS Chicago, Ill.) Variables were ln-transformed when appropriate to obtain a normal distribution. Based upon present evidence, we constructed an analytical model as outlined in Figure 1. We assumed that every variable on a “lower” level could be explained by variables higher up in the hierarchy (e.g. variables at level 5 could be explained by all variables at level 1 – 4). The potential interrelation between variables was first explored in bivariate linear regression analyses, and then subjected to multivariate linear regression analyses. The selection of variables in the multivariate models was based upon results from bivariate analyses, their impact on the coefficients of the other variables, and their theoretical plausibility.

A p-value of < 0.05 was considered statistically significant.

Results

A total of 20 subjects were included in the study, however 2 patients had pulmonary stenosis >3,0 m/s and were excluded. In addition, one patient was found to have previously undiscovered heart vessel abnormalities and was also excluded as a result. The characteristics of the remaining 17 patients are shown in Table 1.

4 patients were operated with a ventriculotomy, the remaining with a transatrial-transpulmonary access.

8 patients were operated with a transannular patch (TAP), the remaining using a combination of infundibulotomy, commisurotomy, and resection of the infundibulum. In 1 patient we were unable to retrieve all details about the surgical technique used for correction because the surgery was performed abroad

12 patients were intitally palliated with a shunt prior to primary repair, 11 with a modified Blalock-Taussig, 1 with Waterstone type.

Ambulatory 24 hour electrocardiography recording was considered normal in all patients; isolated ectopic beats were the only arrhythmias detected. All patients were in sinus rhythm, and all but one had right bundle branch block. Wall motion abnormality of the right ventricular outflow tract was found in 10 patients, 6 of whom had a TAP

The main findings from the multivariate analyses are shown in Figure 2.

Patients with a TAP had a larger PR fraction (r=18.82 (1.18;36.46), p= 0.038) (Table 2). No other surgical variable included in the study correlated to PR.

In bivariate analysis, PR and dyskinesia/akinesia in RVOT correlated with RVEDV (r = 1.50 (0.10;2.01), p=0.000 and, r =3 1.88 (-0.13:63.90), p=0.051 respectively), but only PR remained significant in multivariate analyses, (r=1.37 (0.86;1.88), p=0.000) (Table 3). Ventriculotomy, TAP, additional surgery after repair and dyskinesia in the RVOT correlated to RVEF in bivariate analyses (Table 4), but the relations did not reach statistical significance in multivariate analysis. No explanatory variables correlated to autonomic heart rate control (Table 5). RVEDV was the only variable correlating with QRS duration (r=0.40 (0.11;0.70), p=0.011) (Table 6).

Discussion

The main result from this study is a strong, positive relation between the use of a TAP, PR, RVEDV and QRS-duration. No other relations between variables reached statistical significance in multivariate analyses.

Supporting these findings, previous studies by van den Berg et al (10) and Davlouros et al (4), both found that the use of TAP was the most important predictor of PR severity. Gatzoulis et al found that patients who had a transannular patch type repair were more likely to develop sustained ventricular tachycardia and sudden cardiac death, and that a QRS-duration of >180ms was a risk factor for adverse outcome (3). Our study, showing the relationship between dilatation of the RV and prolongation of the QRS-complex, provides further insight to the hemodynamic mechanisms behind these findings as our patients were investigated with CMR. CMR is an accurate method to evaluate RV volumes and function with good intra- and interobserver reproducibility (11).

Dyskinesia/akinesia in the RVOT has been suggested as an independent contributor to RV dilatation (12). Our data, however, does not confirm this relation.

An increase in RVEDV was not associated with a decreased RVEF in our study although previous studies have shown this correlation. This might be due to a longer interval since repair in these studies.

Other studies have showed that the finding of dyskinetic/akinetic areas in the RVOT is a predictor of a decrease in RVEF (4,10). Furthermore, Van den Berg et al reported a higher incidence of dyskinetic/akinetic RVOT areas in patients with a TAP(10). In our study, we found similar tendencies, as RVEF was negatively correlated with dyskinetic/akinetic RVOT area, ventriculotomy and the use of TAP; however, neither of the relations reached statistical significance.

Older age at repair (1) and a longer interval since repair (2,10) has previously been associated with a worse clinical outcome in several studies. In our study, however, no one of these variables were correlated to PR, RVEDV, RVEF, HFabs or QRS-duration. Neither did pulmonary stenosis prior to repair, palliation prior to repair nor additional surgery after repair. Furthermore, with regards to autonomic heart rate control, we found no correlations to any of the variables included in the study. This is somewhat surprising, as patients operated for ToF previously have been shown to have altered autonomic heart rate control compared to healthy controls (13), thus indicating that alteration of heart rate control only plays a limited part in the arrhythmogenesis in these patients.

Many centres now perform primary repair of ToF at a younger age to prevent damage to the myocardium from long-standing hypoxia and pressure overload. However, this might increase the need for transannular patching. Consequently, several studies reported an increased need for a TAP in younger patients (14,15,16), as well as a higher incidence of restenosing of the RVOT, even in patients with a TAP (14). Seen in conjunction with our findings, one might be concerned that he potential benefits of early primary repair might be outweighed by increased tendency to pulmonary regurgitation, right ventricular dilatation and malignant arrhythmia late after repair. Instead, increased attention should be paid to recent techniques developed for preserving the annular ring (17,18). Long-term follow-up studies of such treatment strategies are an important area for further research.

Study limitations:

This was a retrospective study, obviously leading to less control over surgical variables. Also, due to a limited number of subjects, there is a chance of missing correlations between variables.

We did not analyze the use of other types of patches e.g. right ventricular outflow patch, so their influence is not discovered by our study.

Conclusion:

The use of a transannular patch was the only surgical variable associated with pulmonary regurgitation in our study, in turn leading to right ventricular dilatation and prolongation of the QRS complex.

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Table 1

	Patients	
	n/total	*Percent*
Male gender	11/17	59
Palliation	12/17	71
Ventriculotomy at repair	4/16[a]	24
Transannular patch at repair	8/17	47
Pulmonary replacement after repair	2/17	12
Dyskinesia/Akinesia in RVOT	10/17	59
Pulmonary stenosis prior to repair (m/s)	4.1	(2.5-4.8)
	Median	*Range*
Age (years)	16	(13-18)
Age at repair (years)	2.8	(2-4.2)
Interval since repair (years)	12.8	(10.7-16.4)
Body surface area (m^2)	1.68	(1.42-1.86)
Pulmonary stenosis (m/s)	1.67	(1.25-2.38)
Pulmonary regurgitation (%)	25	(0-60)
Right ventricle end diastolic volume (ml/m^2)	121	(58-189)
Right ventricle ejection fraction (%)	45	(35-66)
QRS duration	132	(76-160)
NT-proBNP (pmol/L)	9.0	(3.8-24.30)
HFabs	615.45	(24.91-4517.99)
Maximum exercise capacity (% of expected O_2 consumption)	71	(49-97)

a) in 1 record, the records didn't explicitly say whether or not a ventriculotomy had been used

Table 2. Relation between background variables (level 1) and pulmonary insufficiency (PI).

	Bivariate regression analyses		**Multivariate regression analyses**	
	Regression coefficient (95 % confidence interval)	p-value	Regression coefficient (95 % confidence interval)	p-value
Gender	9.152 (-11.613-29.916)	0.362		
Pulmonary stenosis prior to repair	11.799 (-6.815-30.413)	0.192		
Palliation prior to repair	1.433 (-20.962-23.829)	0.893		
Age at repair	3.388 (-12.281-19.058)	0.651		
Ventriculotomy	5.417 (-19.680-30.513)	0.651		
Transannular patch	18.819 (1.178-36.461)	0.038		
Years since repair	-1.318 (-6.408-3.772)	0.589		
Additonal surgery after repair	-3.300 (10.948-32.652)	0.827		
Dyskinetic area in RVOT	12.357 (-7.244-31-958)	0.199		

Table 3. Relation between background variables (level 1 and 2) and right ventricular end diastolic volume (RVEDVind).

	Bivariate regression analyses		**Multivariate regression analyses**	
	Regression coefficient (95 % confidence interval)	p-value	Regression coefficient (95 % confidence interval)	p-value
Gender	11.855 (-25.172-48.882)	0.505		
Pulmonary stenosis prior to repair	5.524 (-26.400-37.449)	0.713		
Palliation prior to repair	-7.089 (-46.328-32.150)	0.706		
Age at repair	7.455 (-20.008-34.917)	0.571		
Ventriculotomy	11.573 (-32.347-55.492)	0.581		
Transannular patch	21.825 (12.108-55.759)	0.191		
Years since repair	-0.190 (-9.236-8.856)	0.965		
Additonal surgery after repair	-1.104 (-56.867-54.659)	0.967		
Dyskinetic area in RVOT	31.884 (-0.130-63.898)	0.051	14.942 (-4.237-34.121)	0.117
Pulmonary insufficiency	1.501 (0.996-2.006)	0.000	1.371 (0.862-1.880)	0.000

Table 4. Relation between background variables (level 1-3) and right ventricular ejection fraction (RVEF)

	Bivariate regression analyses		**Multivariate regression analyses**	
	Regression coefficient (95 % confidence interval)	p-value	Regression coefficient (95 % confidence interval)	p-value
Gender	-1.379 (-11.563-8.806)	0.777		
Pulmonary stenosis prior to repair	1.138 (-6.699-9.975)	0.757		
Palliation prior to repair	-4.450 (-14.877-5.977)	0.377		
Age at repair	-2.446 (-9.868-4.975)	0.493		
Ventriculotomy	8.667 (-1.702-19.036)	0.095	7.126 (-3.054-17.306)	0.153
Transannular patch	-8.139 (-16.830-0.553)	0.064	-4.355 (-13.558-4.849)	0.323
Years since repair	0.907 (-1.500-3.313)	0.435		
Additonal surgery after repair	-11.400 (-25.187-2.387)	0.098		
Dyskinetic area in RVOT	-7.914 (-16.823-0.995)	0.078	-5.420 (14.426-3.586)	0.214
Pulmonary insufficiency	-0.075 (-3.335-0.185)	0.546		
Right ventricular end diastolic volume	-0.053 (-0.199-0.094)	0.454		

Table 5. Relation between background variables (level 1-4) and high frequency-variability of heart rate, HFabs

	Bivariate regression analyses		Multivariate regression analyses	
	Regression coefficient (95 % confidence interval)	p-value	Regression coefficient (95 % confidence interval)	p-value
Gender	1.110 (-0.414-2.634)	0.140		
Pulmonary stenosis prior to repair	19.316 (-1.606-1.579)	0.986		
Palliation prior to repair	0.913 (-0.773-2.598)	0.263		
Age at repair	0.511 (0.677-1.699)	0.370		
Ventriculotomy	0.273 (-1.773-2.319)	0.776		
Transannular patch	0.525 (-1.043-2.094)	0.482		
Years since repair	-0.006 (-0.385-0.372)	0.971		
Additonal surgery after repair	0.534 (-1.749-2.817))	0.622		
Dyskinetic area in RVOT	0.044 (-1.556-1.643)	0.954		
Pulmonary insufficiency	-0.003 (-0.044-0.039)	0.892		
Right ventricular end diastolic volume	0.006 (-0.017-0.029)	0.607		
Right ventricular ejection fraction	0.016 (-0.073-0.105)	0.708		

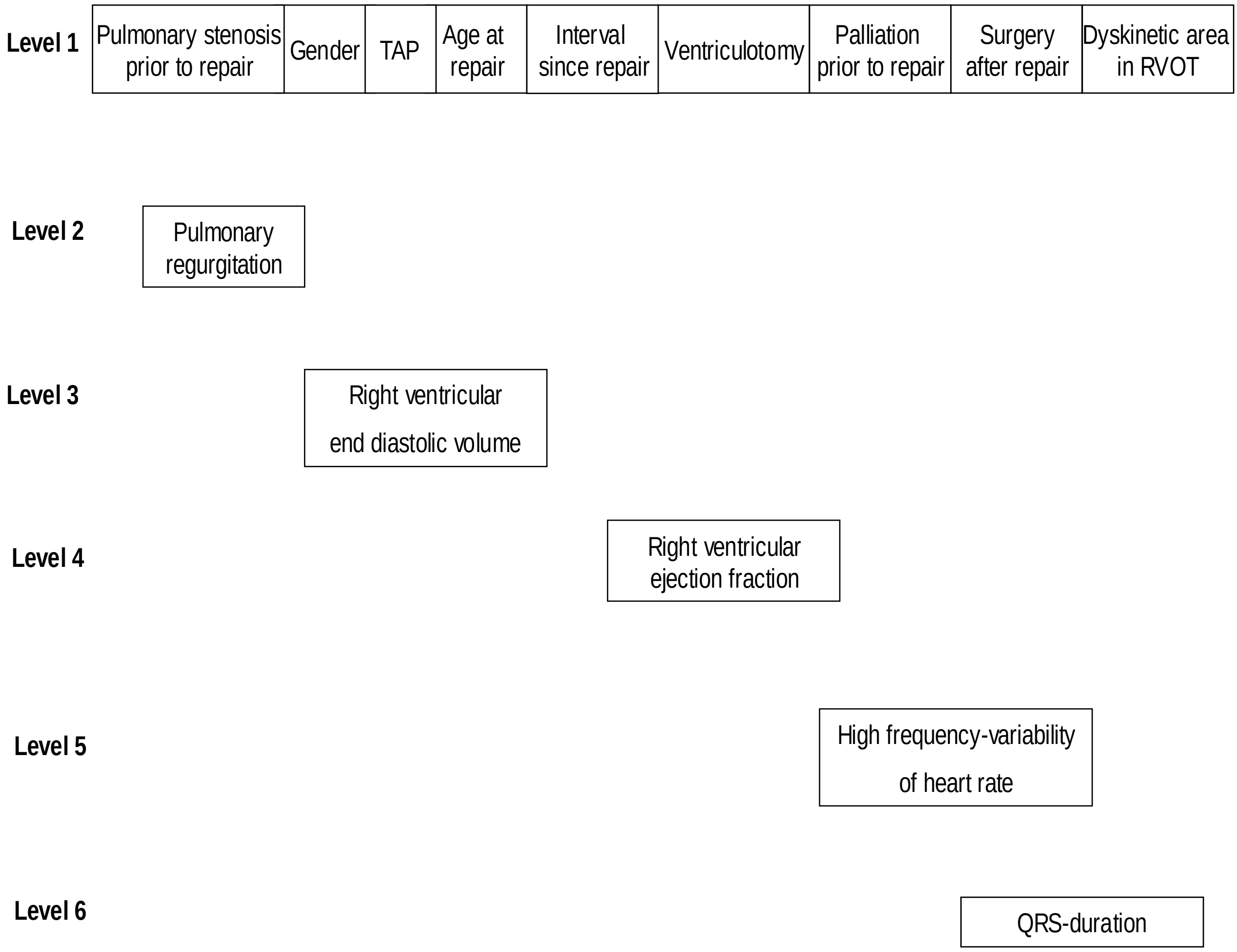
Table 6. Relation between background variables (level 1-5) and QRS-duration

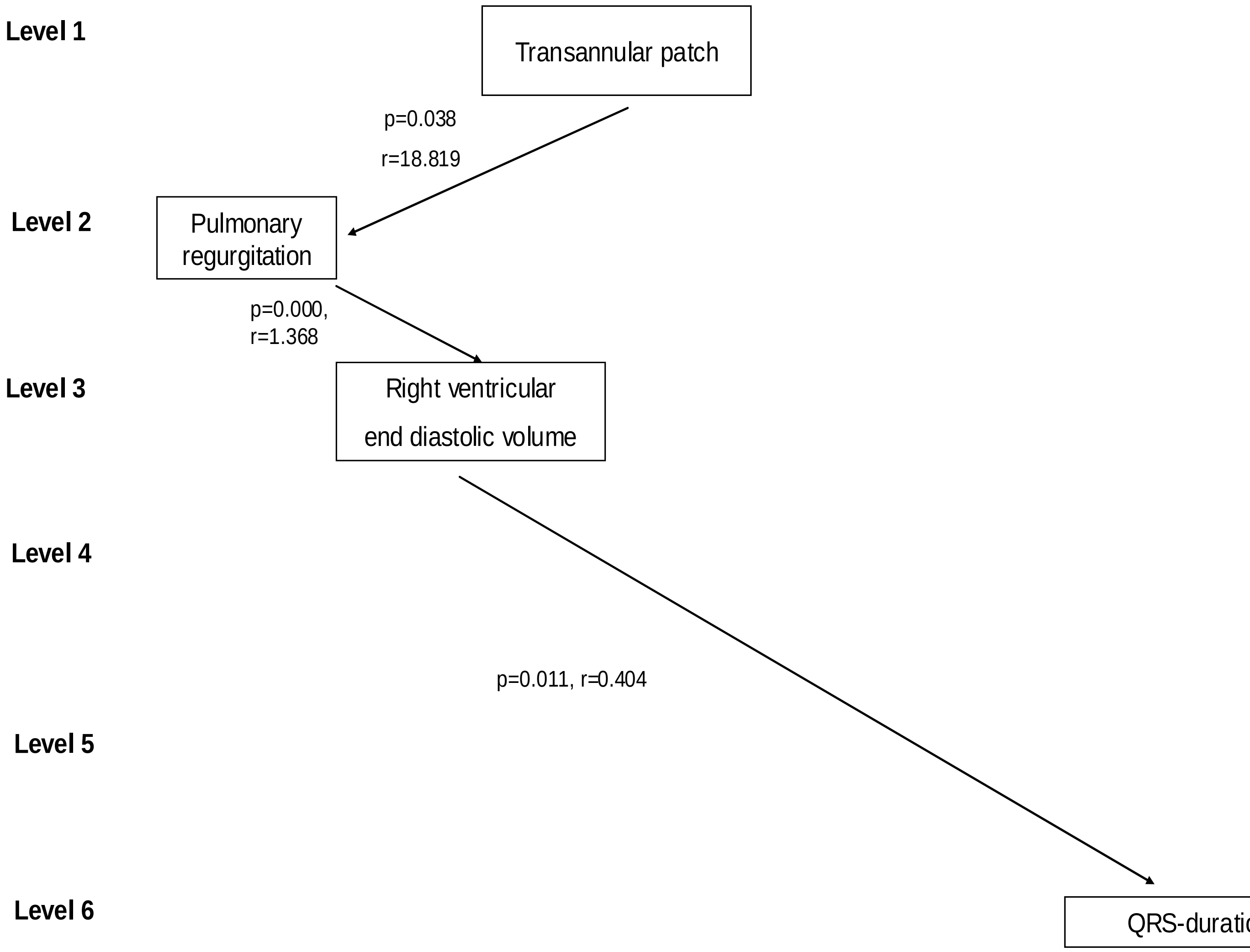
	Bivariate regression analyses		**Multivariate regression analyses**	
	Regression coefficient (95 % confidence interval)	p-value	Regression coefficient (95 % confidence interval)	p-value
Gender	15.485 (-8.863-39.833)	0.195		
Pulmonary stenosis prior to repair	-6.178 (-32.467-20.111)	0.618		
Palliation prior to repair	-2.767 (-29.779-24.246)	0.830		
Age at repair	2.707 (-16.286-21.701)	0.765		
Ventriculotomy	13.167 (-15.263-41.597)	0.337		
Transannular patch	19.556 (-2.674-41.785)	0.080	10.743 (-8.598-30.084)	0.253
Years since repair	-0.097 (-6.304-6.109)	0.974		
Additonal surgery after repair	16.267 (-20.933-53.466)	0.366		
Dyskinetic area in RVOT	17.857 (-55.183-40.897)	0.119		
Pulmonary insufficiency	0.494 (-0.112-1.100)	0.103		
Right ventricular end diastolic volume	0.459 (0.278-0.739)	0.003	0.404 (0.108-0.699)	0.011
Right ventricular ejection fraction	-0.022 (-1.412-1.368)	0.973		
High frequency variability of heart rate	7.242 (-1.696-16.179)	0.104		

Figure legends:

Figure 1: Analytical model of our study. We assumed that each variable on a lower level could be explained by a variable on a higher level. The interrelations between variables were explored with bivariate followed by multivariate regression analyses.

Figure 2: Summary of our findings in multivariate regression analyses, suggesting a causal relationship between the use of a transannular patch, pulmonary regurgitation dilatation of the right ventricle and prolongation of the QRS complex.


Level 1
Pulmonary stenosis prior to repair
Gender
TAP
Age at repair
Interval since repair
Ventriculotomy
Palliation prior to repair
Surgery after repair
Dyskinetic area in RVOT
Level 2
Pulmonary regurgitation
Level 3
Right ventricular end diastolic volume
Level 4
Right ventricular ejection fraction
Level 5
High frequency-variability of heart rate
Level 6
QRS-duration


Level 1
Transannular patch
p=0.038
r=18.819
Level 2
Pulmonary regurgitation
p=0.000,
r=1.368
Level 3
Right ventricular
end diastolic volume
Level 4
p=0.011, r=0.404
Level 5
Level 6
QRS-duratio